Expedient Synthesis of Biginelli-Type Dihydropyrimidinones Using α-(Benzotriazolyl)alkyl Urea Derivatives

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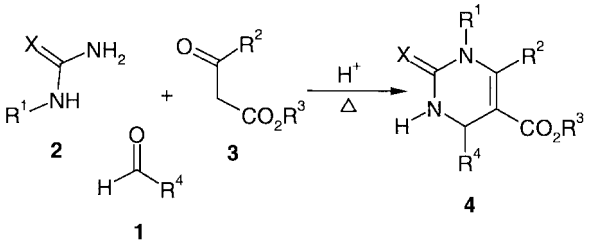
Abstract: Reaction of readily available α-(benzotriazolyl)alkyl urea derivatives (derived from aromatic, heteroaromatic, and aliphatic aldehydes) with β-keto esters resulted in 3,4-dihydropyrimidin-2(1*H*)-ones in good to excellent yields.

Key words: urea, heterocycles, pyrimidines, condensation, esters, cyclizations

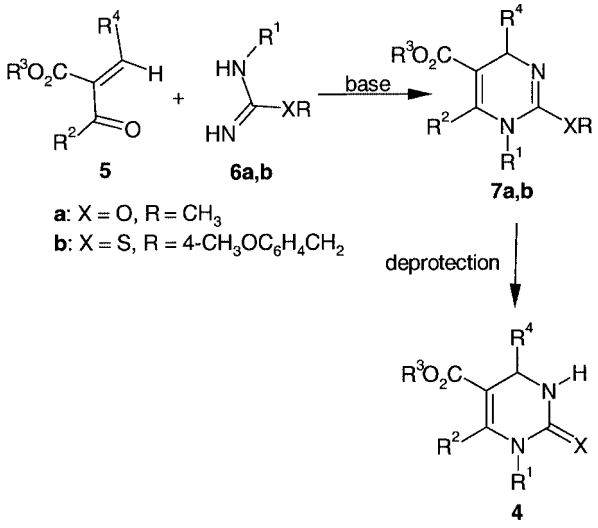
In recent years, there has been increasing interest in the synthesis of alkyl dihydropyrimidine-5-carboxlates (DHPMs)[1] of type **4**. This stems from their close structural relationship to clinically important 1,4-dihydropyridine calcium channel modulators of the type nifedipine etc. Also, dihydropyrimidinone derivatives exhibit a similar pharmacological profile to DHP.[1–4] Some dihydropyrimidinone uses are: α_{a1} adrenoaceptor-selective antagonists,[5] anticancer drugs capable of inhibiting kinesin motor protein,[6] calcium channel blockers and antihypertensives,[3,7] and also for the treatment of benign prostatic hyperlasia.[8] Several marine-derived natural products such as crambine, batzelladine B (potent HIV gp-120CD4 inhibitors) and ptilomycelin A[9–11] alkaloids also contain the dihydropyrimidinone-5-carboxlate core.

The most simple and straightforward procedure for the synthesis of dihydropyrimidinones reported by P. Biginelli in 1893, involves the acid-catalyzed condensation of a β-keto ester **3** with an aromatic aldehyde **1** and urea derivative **2** (Scheme 1).[12,13] The major drawback associated with this protocol is the low yields, particularly in the case of aliphatic or substituted aromatic aldehydes.[13,14] This has led to the development of multi-step synthetic strategies that produce somewhat better yields but lack the simplicity of the one-pot, one-step synthesis[14–16] (Scheme 2).

Recently, Biginelli dihydropyrimidinone synthesis has received great interest in order to improve the efficiency of the procedure. Lewis acids ($BF_3{\cdot}Et_2O$,[17] $FeCl_3{\cdot}6\ H_2O$,[18] $LaCl_3{\cdot}7\ H_2O$,[19] polyphosphate ester (PPE),[20] acidic clay montmorillonite KSF,[21] manganese(III) acetate,[22] ytterbium (III)-resin,[23] 1-butyl-3-methylimidazolium tetrafluoroborate ($BMImBF_4$) or hexafluorophosphate ($BMImPF_6$),[24] lanthanide triflate,[25] zirconium chloride,[26] and indium chloride[27] were employed as catalysts for the one-pot syntheses of DHPMs. More recently, microwave[28] has also been used to assist Biginelli condensation. The yields quoted in the literature[17–22,24] of 53–99% (average 76%) are based on the amount of either aldehyde or β-keto ester utilized, whereas recalculation based on the amount of urea used gives yields 35–66% (average 51%). However, in the procedure of one reference[23] a 1:1:3 ratio of reagents gave yields of 20–27% (average 24%) based on the amount of reagent, a three fold excess was used.



Scheme 1



Scheme 2

Benzotriazole has been emphasized as a new synthetic auxiliary that offers many advantages.[29] *N*-(α-Amidoalkyl)benzotriazoles have been used as powerful reagents for the *N*-amidoalkylation of amines,[30] *O*-amidoalkylation of alcohols,[31] *S*-amidoalkylation of mercaptans,[32] and *C*-amidoalkylation of CH-acidic,[33] electron-rich aromatic compounds,[34] and deactivated

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olefins.[35] This offered some clues that reaction of α-benzotriazolated urea with a β-keto ester could be a possible modification of the Biginelli reaction that produces high yields of the target dihydropyrimidines. We now report the reaction of α-(benzotriazolyl)alkyl urea derivatives with a β-keto ester, which provides a convenient route for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones **4a**–**q** in yields of 77–97% (average 87%) based on using the reagents in a 1:1 ratio.

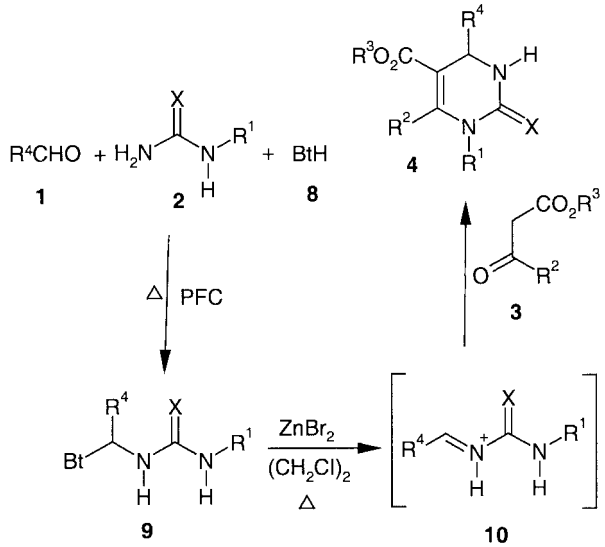
Treatment of α-(benzotriazolyl)alkyl urea derivatives **9a**–**j**, which were prepared in excellent yields by the condensation of benzotriazole, an aldehyde, and urea in performance fluids in the presence of Amberlyst® 15 resin with azeotropic removal of water as previously reported[36] (Scheme 3), with β-keto esters **3a**–**c** in the presence of zinc bromide in refluxing 1,2-dichloroethane afforded the corresponding alkyl 3,4-dihydropyrimidine-5-carboxlates **4a**–**q** (Scheme 3, Table 1). The TLC and NMR of the crude products show that the reactions are very clean; usually benzotriazole is the only byproduct, and occasionally, small amounts of unreacted β-keto ester **3** were detected. This synthetic route provided the previously known compounds **4a**,**q** in comparable yields with those reported in the literature.[25,28] The yields of previously unreported **4b**–**p** were 81–97%. Several adducts **9** derived from aromatic aldehydes containing either electron-donating or electron-withdrawing groups were examined. Furthermore, the reactivity of benzotriazole adducts **9** derived from heteroaromatic and aliphatic aldehydes with β-keto esters in the presence of a Lewis acid was also examined. In all cases, the reaction proceeded smoothly to give the corresponding dihydropyrimidinones in high yield. Compared to the classical Biginelli method, one important feature of the present protocol is the ability to tolerate variation in all the reaction components.

NMR spectroscopy and elemental analyses supported the structures of the dihydropyrimidineones **4a**–**q**. The ^{1}H NMR spectra of the compounds **4a**–**q** showed two characteristic signals in the region δ = 5.75–8.62 and 5.46–6.36, ppm which were assigned to the proton type attached to the nitrogen at the 3-position and the methine proton type attached to the carbon at 4-position, respectively. In the ^{13}C NMR spectra, the carbonyl groups of both ester and imide in compounds **4a**–**o**,**q** exhibited signals in the regions δ = 164.5–166.4, 153.2–156.0 ppm, and the tertiary carbon at 4-position showed a signal in the region δ = 51.3–60.4 ppm.

The Lewis acid used in this reaction as a catalyst is inexpensive, easily available and highly efficient for this transformation. The reaction may proceed through the acylimine intermediate [generated in situ by the displacement of the benzotriazolyl moiety from α-(benzotriazolyl)alkyl urea **9**], which is stabilized by the zinc ion, and the subsequent addition of the β-keto ester enloate to the acylimine followed by cyclization and dehydration, affords the corresponding dihydropyrimidinones.

This new synthetic procedure for the preparation of dihydropyrimidinones offers advantages. It has demonstrated good generality: it could be used with α-(benzotriazolyl)alkyl urea derived from aromatic aldehydes containing either electron-donating or electron-withdrawing groups (to give **4a**–**m**), heteroaromatic aldehydes (to give **4n**–**p**), and an aliphatic aldehyde (to give **4q**). It utilizes easily prepared α-(benzotriazolyl)alkyl as ureidoalkylating reagents, and the by product (benzotriazole) can be easily removed by washing with saturated aqueous Na_2CO_3.

In summary, the use of α-(benzotriazolyl)alkyl ureas **9** as a masked acyliminium ion in the reaction with β-keto esters provides a simple and convenient method particularly for the preparation of C6-aryl substituted Biginelli compounds. The adopted procedure is effective, involves simple experimental procedures and product isolation; hence, it is a useful addition to the existing synthetic methods.



Scheme 3 For designation of R^1, R^2, R^3, R^3, and X in **4** see Table 1

All mps are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini (300 MHz) spectrometer in $CDCl_3$, DMSO-d_6 or Me_2CO-d_6 with TMS as the internal standard. Microanalyses were performed on a Carlo Erba 1106 elemental analyzer.

Benzotriazole Derivatives 9; General Procedure

A mixture of benzotriazole (1.19 g, 10 mmol), aldehyde (10 mmol), urea (10 mmol) and acidic cationic resin Amberlyst® 15 (0.1 g) was heated under reflux together with performance fluid (15 mL; available from the 3M company) in a 50 mL round-bottom flask fitted with a Dean–Stark trap. After refluxing for 12 h, H_2O (0.2 mL) was removed. Then the mixture was allowed to cool and the crude product was removed from the performance fluid by decantation. The product was dissolved in benzene (100 mL), the resin filtered off and the solvent removed to give **9** as low melting solids in 80–90% yields with 94–97% purity (as estimated by ^{1}H and ^{13}C NMR), which were used as such for further reaction.

Alkyl 3,4-Dihydropyrimidin-2(1*H*)-one-5-carboxlates 4a–q; General Procedure

A mixture of α-(benzotriazolyl)alkyl urea 9 (2 mmol), β-keto ester (2 mmol) and zinc bromide (4 mmol) in anhydrous 1,2-dichloro-

Table 1 Synthesis of Alkyl 3,4-Dihydropyrimidine-5-carboxlates **4a**–**q** via Ureidoalkyation of β-Keto Esters **3** with α-(Benzotriazolyl)alkyl Urea Derivatives **9**

Entry	R^1	R^2	R^3	R^4	X	Yield (%)	Lit. yield (%)
4a	Me	Me	Et	Ph	O	85	89[28]
4b	Me	Ph	Et	Ph	O	91	–
4c	Me	Ph	Et	4-MeC_6H_4	O	81	–
4d	Me	Me	Me	1-Naphthyl	O	84	–
4e	Me	Ph	Et	1-Naphthyl	O	90	–
4f	Me	Me	Me	2-MeO-5-BrC_6H_3	O	89	–
4g	Me	Ph	Et	2-MeO-5-BrC_6H_3	O	93	–
4h	Me	Me	Me	4-ClC_6H_4	O	92	–
4i	Me	Ph	Et	4-ClC_6H_4	O	94	–
4j	Me	Me	Me	4-CNC_6H_4	O	81	–
4k	Me	Ph	Et	4-CNC_6H_4	O	85	–
4l	Me	Me	Et	4-$NO_2C_6H_4$	O	89	–
4m	Me	Ph	Et	4-$NO_2C_6H_4$	O	97	–
4n	Me	Me	Me	2-Thienyl	O	82	–
4o	Me	Ph	Et	2-Thienyl	O	91	–
4p	H	Me	Me	2-Thienyl	S	85	–
4q	H	Me	Et	$CHMe_2$	O	77	83[25]

ethane (20 mL) was refluxed for 24 h and poured into ice–H_2O (50 mL), then extracted with EtOAc (3 × 20 mL). The combined organic extract was washed with sat. aq Na_2CO_3 (40 mL) and H_2O (30 mL) and dried ($MgSO_4$, 5 g). The solvent was removed in vacuo and the resulting oil was purified by column chromatography (silica gel; CH_2Cl_2–EtOAc, 4:1) or by recrystallization from EtOH to give products **4a**–**q**.

Ethyl 1,6-Dimethyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4a)
Yield: 0.47 g (85%); colorless microcrystals; mp 176–177 °C (lit.[28] 180 °C).

^{1}H NMR: δ = 7.32–7.24 (m, 5 H), 5.75 (br s, 1 H), 5.39 (d, 1 H, *J* = 3.2 Hz), 4.11 (q, 2 H, *J* = 7.1 Hz), 3.2 (s, 3 H), 2.52 (s, 3 H), 1.19 (t, 3 H, *J* = 7.1 Hz).

^{13}C NMR: δ = 166.0, 154.1, 149.3, 143.3, 128.6, 127.6, 126.1, 104.1, 60.1, 53.6, 30.2, 16.4, 14.1.

Ethyl 4,6-Diphenyl-1-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4b)
Yield: 0.61 g (91%); colorless microcrystals; mp 162–164 °C.

^{1}H NMR: δ = 7.41–7.22 (m, 10 H), 6.12 (br s, 1 H), 5.49 (d, 1 H, *J* = 3.2 Hz), 3.79 (q, 2 H, *J* = 7.1 Hz), 2.80 (s, 3 H), 0.78 (t, 3 H, *J* = 7.1 Hz).

^{13}C NMR: δ = 165.3, 154.2, 150.4, 143.3, 134.8, 128.8, 128.4, 128.2, 127.9, 127.3, 126.2, 105.3, 59.9, 54.1, 32.4, 13.4.

Anal. Calcd for $C_{20}H_{20}N_2O_3$ (336.39): C, 71.41; H, 5.99; N, 8.33. Found C, 71.70; H, 5.81; N, 8.14.

Ethyl 1-Methyl-4-(4-methylphenyl)-2-oxo-6-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4c)
Yield: 0.57 g (81%); colorless microcrystals; mp 223–225 °C.

^{1}H NMR: δ = 7.41–7.14 (m, 9 H), 5.95 (br s, 1 H), 5.45 (d, 1 H, *J* = 1.8 Hz), 3.78 (q, 2 H, *J* = 7.1 Hz), 2.80 (s, 3 H), 2.34 (s, 3 H), 0.77 (t, 3 H, *J* = 7.1 Hz).

^{13}C NMR: δ = 165.3, 154.1, 150.2, 140.4, 137.6, 134.9, 129.4, 128.7, 128.2, 127.4, 126.2, 105.5, 59.9, 54.9, 32.4, 21.1, 13.4.

Anal. Calcd for $C_{21}H_{22}N_2O_3$ (350.42): C, 71.98; H, 6.33; N, 7.99. Found C, 71.76; H, 6.49; N, 8.12.

Methyl 1,6-Dimethyl-4-(1-naphthyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4d)
Yield: 0.52 g (84%); colorless plates; mp 177–179 °C.

^{1}H NMR: δ = 8.17 (d, 1 H, *J* = 8.2 Hz), 7.87 (d, 1 H, *J* = 8.2 Hz), 7.76 (d, 1 H, *J* = 8.0 Hz), 7.58–7.49 (m, 2 H), 7.41–7.30 (m, 2 H), 6.22 (br s, 1 H), 5.89 (br s, 1 H), 3.47 (s, 3 H), 3.47 (s, 3 H), 2.65 (s, 3 H).

^{13}C NMR: δ = 166.4, 153.5, 150.7, 137.3, 134.2, 130.2, 129.2, 128.6, 126.6, 125.7, 125.6, 123.6, 122.0, 102.3, 51.3, 49.4, 30.2, 16.5.

Anal. Calcd for $C_{18}H_{18}N_2O_3$ (310.36): C, 69.66; H, 5.85; N, 9.03. Found C, 69.45; H, 6.09; N, 8.89.

Ethyl 1-Methyl-4-(1-naphthyl)-2-oxo-6-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4e)
Yield: 0.67 g (90%); pale yellow plates; mp 193–195 °C.

^{1}H NMR: δ = 8.07 (d, 1 H, *J* = 8.4 Hz), 7.88 (d, 1 H, *J* = 8.0 Hz), 7.81 (d, 1 H, *J* = 8.1 Hz), 7.63–7.24 (m, 9 H), 6.33 (br s, 1 H), 6.06 (br s, 1 H), 3.67 (q, 2 H, *J* = 7.1 Hz), 2.81 (s, 3 H), 0.62 (t, 3 H, *J* = 7.1 Hz).

^{13}C NMR: δ = 165.1, 153.5, 151.2,137.6, 134.9, 134.2, 130.3, 129.1, 128.8, 128.7, 128.6, 128.3, 126.6, 125.7, 125.6, 123.8, 122.3, 103.9, 59.8, 50.0, 32.2, 13.3.

Anal. Calcd for $C_{23}H_{20}N_2O_3$ (372.43): C, 74.18; H, 5.41; N, 7.52. Found C, 73.93; H, 5.63; N, 7.69.

Methyl 1,6-Dimethyl-4-(5-bromo-2-methoxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4f)
Yield: 0.66 g (89%); colorless microcrystals; mp 150–152 °C.

^{1}H NMR: δ = 7.34 (d, 1 H, *J* = 8.7 Hz), 7.03 (s, 1 H), 6.76 (d, 1 H, *J* = 8.8 Hz), 5.94 (br s, 1 H), 5.60 (s, 1 H), 3.84 (s, 3 H), 3.62 (s, 3 H), 3.19 (s, 3 H), 2.64 (s, 3 H).

^{13}C NMR: δ = 166.2, 156.0, 153.9, 152.1, 131.7, 131.4, 128.9, 112.9, 112.3, 100.1, 55.5, 51.4, 48.2, 30.3, 16.5.

Anal. Calcd for $C_{15}H_{17}BrN_2O_4$ (369.22): C, 48.80; H, 4.64; N, 7.59. Found C, 49.07; H, 4.39; N, 7.80.

Ethyl 4-(5-Bromo-2-methoxyphenyl)-1-methyl-2-oxo-6-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4g)
Yield: 0.83 g (93%); colorless plates; mp 179–181 °C.

^{1}H NMR: δ = 7.47–7.25 (m, 7 H), 6.80 (d, 1 H, *J* = 8.7 Hz), 5.91 (br s, 1 H), 5.68 (d, 1 H, *J* = 3.7 Hz), 3.80 (q, 2 H, *J* = 7.1 Hz,), 2.78 (s, 3 H), 0.78 (t, 3 H, *J* = 7.1 Hz).

^{13}C NMR: δ = 165.0, 156.2, 154.0, 152.6, 134.9, 131.8, 131.4, 129.4, 128.9, 128.6, 127.3, 113.0, 112.6, 101.5, 59.9, 55.7, 48.9, 32.4, 13.4.

Anal. Calcd for $C_{21}H_{21}BrN_2O_4$ (445.32): C, 56.64; H, 4.75; N, 6.29. Found C, 56.78; H, 4.69; N, 5.97.

Methyl 4-(4-Chlorophenyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4h)
Yield: 0.54 g (92%); colorless plates; mp 117–119 °C.

^{1}H NMR: δ = 7.26 (d, 2 H, *J* = 8.2 Hz), 7.17 (d, 2 H, *J* = 7.8 Hz), 6.30 (br s, 1 H), 5.36 (s, 1 H), 3.66 (s, 3 H), 3.21 (s, 3 H), 2.51 (s, 3 H).

^{13}C NMR: δ = 166.3, 154.0, 149.9, 141.7, 133.5, 128.8, 127.5, 103.6, 52.9, 51.4, 30.3, 16.6.

Anal. Calcd for $C_{14}H_{15}ClN_2O_3$ (294.74): C, 57.05; H, 5.13. Found C, 56.88; H, 5.06.

Ethyl 4-(4-Chlorophenyl)-1-methyl-6-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4i)
Yield: 0.70 g (94%); colorless microcrystals; mp 203–205 °C.

^{1}H NMR: δ = 7.42–7.19 (m, 9 H), 6.18 (br s, 1 H), 5.47 (d, 1 H, *J* = 3.3 Hz), 3.79 (q, 2 H, *J* = 7.1 Hz), 2.80 (s, 3 H), 0.76 (t, 3 H, *J* = 7.1 Hz).

^{13}C NMR: δ = 165.3, 154.1, 150.6, 141.8, 134.6, 133.6, 128.9, 128.5, 128.3, 127.7, 127.3, 105.1, 60.0, 53.5, 32.5, 13.4.

Anal. Calcd for $C_{20}H_{19}ClN_2O_3$ (370.84): C, 64.78; H, 5.16; N, 7.55. Found C, 64.69; H, 5.13; N, 7.34.

Methyl 4-(4-Cyanophenyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4j)
Yield: 0.46 g (81%); pale yellow needles; mp 162–164 °C.

^{1}H NMR: δ = 7.60–7.36 (m, 4 H), 6.95 (br s, 1 H), 5.44 (d, 1 H, *J* = 3.7 Hz), 3.67 (s, 3 H), 3.20 (s, 3 H), 2.52 (s, 3 H).

^{13}C NMR: δ = 166.1, 154.0, 150.6, 148.2, 132.4, 126.8, 118.5, 111.4, 102.8, 52.9, 51.4, 30.3, 16.5.

Anal. Calcd for $C_{15}H_{15}N_3O_3$ (285.31): C, 63.15; H, 5.30; N, 14.73. Found C, 62.97; H, 5.19; N, 14.66.

Ethyl 4-(4-Cyanophenyl)-1-methyl-2-oxo-6-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4k)
Yield: 0.61 g (85%); colorless needles; mp 187–189 °C.

^{1}H NMR: δ = 7.67 (d, 2 H, *J* = 8.2 Hz), 7.56 (d, 2 H, *J* = 8.1 Hz), 7.46–7.27 (m 3 H), 7.21–7.15 (m, 2 H), 6.63 (d, 1 H, *J* = 3.2 Hz), 5.56 (d, 1 H, *J* = 3.6 Hz), 3.79 (q, 2 H, *J* = 7.1 Hz), 2.80 (s, 3 H), 0.74 (t, 3 H, *J* = 7.1 Hz).

^{13}C NMR: δ = 165.2, 154.1, 151.3, 148.3, 134.3, 132.6, 129.0, 128.5, 128.3, 127.3, 127.0, 111.7, 104.5, 60.2, 53.6, 32.5, 13.3.

Anal. Calcd for $C_{21}H_{19}N_3O_3$ (361.40): C, 69.79; H, 5.30; N, 11.63. Found C, 69.93; H, 5.13; N, 11.57.

Ethyl 1,6-Dimethyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4l)
Yield: 0.54 g (89%); yellow plates; mp 112–114 °C.

^{1}H NMR: δ = 8.14 (d, 2 H, *J* = 8.5 Hz), 7.44 (d, 2 H, *J* = 8.4 Hz), 6.85 (br s, 1 H), 5.51 (d, 1 H, *J* = 3.0 Hz), 4.14 (q, 2 H, *J* = 7.1 Hz), 3.22 (s, 3 H), 2.54 (s, 3 H), 1.21 (t, 3 H, *J* = 7.1 Hz).

^{13}C NMR: δ = 165.6, 154.0, 151.3, 150.3, 147.3, 127.1, 123.9, 103.1, 60.4, 53.0, 30.4, 16.6, 14.1.

Anal. Calcd for $C_{14}H_{15}N_3O_5$ (305.29): C, 55.08; H, 4.95; N, 13.76. Found C, 54.97; H, 5.11; N, 13.84.

Ethyl 1-Methyl-4-(4-nitrophenyl)-2-oxo-6-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4m)
Yield: 0.74 g (97%); colorless plates; mp 190–192 °C.

^{1}H NMR: δ = 8.22 (d, 2 H, *J* = 7.4 Hz), 7.62 (d, 2 H, *J* = 7.6 Hz), 7.44 –7.15 (m, 5 H), 6.86 (br s, 1 H), 5.62 (s, 1 H), 3.80 (q, 2 H, *J* = 7.1 Hz), 2.80 (s, 3 H), 0.77 (t, 3 H, *J* = 7.1 Hz).

^{13}C NMR: δ = 165.2, 154.2, 151.4, 150.3, 147.5, 134.3, 129.1, 128.7, 128.4, 127.2, 124.1, 104.4, 60.2, 53.3, 32.5, 13.3.

Anal. Calcd for $C_{20}H_{19}N_3O_5$ (381.39): C, 62.99; H, 5.02; N, 11.02. Found C, 63.11; H, 5.07; N, 11.23.

Methyl 1,6-Dimethyl-2-oxo-4-(2-thienyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4n)
Yield: 0.44 g (82%); brownish yellow microcrystals; mp 149–151 °C.

^{1}H NMR (DMSO-d_6): δ = 8.14 (d, 1 H, *J* = 3.8 Hz), 7.35 (d, 1 H, *J* = 4.9 Hz), 6.93 (dd, 1 H, *J* = 3.6, 8.4 Hz), 6.88 (br s, 1 H), 5.40 (d, 1 H, *J* = 3.6 Hz), 3.64 (s, 3 H), 3.10 (s, 3 H), 2.47 (s, 3 H).

^{3}C NMR (DMSO-d_6): δ = 165.6, 153.2, 151.3, 147.8, 126.8, 124.7, 123.6, 102.8, 51.2, 48.1, 29.8, 16.0.

Anal. Calcd for $C_{12}H_{14}N_2O_3S$ (266.32): N, 10.52. Found N, 10.29.

Ethyl 1-Methyl-2-oxo-6-phenyl-4-(2-thienyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4o)
Yield: 0.62 g (91%); pale yellow needles; mp 170–172 °C.

^{1}H NMR (DMSO-d_6): δ = 8.29 (d, 1 H, *J* = 3.9 Hz), 7.45–7.41 (m, 4 H), 7.27–6.99 (m, 4 H), 5.47 (d, 1 H, *J* = 3.9 Hz), 3.72 (q, 2 H, *J* = 7.0 Hz), 2.65 (s, 3 H), 0.71 (t, 3 H, *J* = 7.1 Hz).

^{13}C NMR (DMSO-d_6): δ = 164.5, 153.2, 151.0, 147.7, 134.5, 128.7, 128.3, 127.4, 127.0, 125.0, 124.1, 104.4, 59.3, 48.5, 32.0, 13.3.

Anal. Calcd for $C_{18}H_{18}N_2O_3S$ (342.42): C, 63.14; H, 5.30; N, 8.18. Found C, 63.46; H, 5.19; N, 7.99.

Methyl 6-Methyl-4-(2-thienyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4p)
Yield: 0.46 g (85%); brown microcrystals; mp 212–214 °C.

^{1}H NMR (acetone-d_6): δ = 9.47 (br s, 1 H), 8.91 (br s, 1 H), 7.40–6.99 (m, 3 H), 5.74 (s, 1 H), 3.74 (s, 2 H), 2.48 (s, 3 H).

^{13}C NMR (acetone-d_6): δ = 177.0,166.3, 148.0, 146.0, 127.7, 127.6, 126.0, 125.3, 103.0, 60.8, 51.6, 17.8.

Anal. Calcd for $C_{11}H_{12}N_2O_2S_2$ (268.36): N, 10.44. Found N, 10.61.

Ethyl 4-Isopropyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4q)
Yield: 0.35 g (77%); colorless microcrystals; mp 192–194 °C (lit.[25] mp 194–195 °C).

^{1}H NMR: δ = 8.62 (br s, 1 H), 6.36 (br s, 1 H), 4.23–4.13 (m, 3 H), 2.29 (s, 3 H), 1.89–1.83 (m, 1 H), 1.28 (t, 3 H, *J* = 7.1 Hz), 0.92 (d, 3 H, *J* = 6.9 Hz), 0.86 (d, 3 H, *J* = 6.7 Hz).

^{13}C NMR: δ = 166.2, 155.3, 147.1, 100.2, 59.8, 56.8, 34.5, 18.4, 15.6, 14.2.

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